UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/516,741	08/15/2005	Thomas Jespersen	4528-0109PUS2	6986

2292 7590 04/12/2007

BIRCH STEWART KOLASCH & BIRCH
PO BOX 747
FALLS CHURCH, VA 22040-0747

EXAMINER	
WESSENDORF, TERESA D	
ART UNIT	PAPER NUMBER
1639	

SHORTENED STATUTORY PERIOD OF RESPONSE	NOTIFICATION DATE	DELIVERY MODE
3 MONTHS	04/12/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Notice of this Office communication was sent electronically on the above-indicated "Notification Date" and has a shortened statutory period for reply of 3 MONTHS from 04/12/2007.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/516,741	JESPERSEN ET AL.	
	Examiner	Art Unit	
	T. D. Wessendorf	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 7-14* is/are pending in the application.

4a) Of the above claim(s) *3,10,12 and 14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 7-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicants' election with traverse of Group I, claims 1, 2 and 7-13 made on 1/19/2007 is acknowledged. The traversal is on the ground(s) that the claimed method is for performing electrophysiological measurements. As part of this method, it is merely one possible feature that the sequence information is stored on an information carrier, such as a computer disc. Claim 2 relates to the step of sequencing the genetic material and does not mention that the sequence information is stored in any particular manner. Therefore, Claim 3 in which the sequence in formation is stored on a disc serves to narrow the scope of the claims. The unifying inventive concept for all of the claims is in the application of measuring electrophysiological changes due to gene expression and not where the sequence data is stored. This is not found persuasive because while the unifying inventive concept resides on measuring the electrophysiological changes due to gene expression however each of the claims define a contribution over the prior art. Each of the claims is distinct from one another in the means by which the measurement/data is stored e.g., in computer disc. Storing data on a computer disc requires not only special processing but also

a computer media(disc) not required for non-computer storage i.e., paper.

The requirement is still deemed proper and is therefore made FINAL.

Claims 3 and 14 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Applicants timely traversed the restriction (election) requirement on 1/19/2007.

Applicants' election of the species small organic molecules and Chinese Hamster Ovary cells, illustrated in claims 10 and 12, with traverse is also noted.

Applicants believe that the scope of the claims should not be limited to only one compound or cell type, as all are equally suitable for use in this method. Regardless, the election of species should serve as a starting point for search and examination purposes. Upon the indication of allowable subject matter for the elected species, the Examiner is required to expand her search to include other non-elected species with the intent of finding the generic claim(s) ultimately allowable.

Status of Claims

Claims 1-3 and 7-14 are pending

Claims 3, 10 (with respect to the non-elected species), 12 (with respect to the non-elected species) and 14 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention,

Claims 1-2 and 7-13 are under examination.

Specification

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors (typographical, grammatical and idiomatic). Applicants' cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2 and 7-13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably

convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

To satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the genus of the invention.

The specification fails to adequately describe the claimed generic method. The specification provides only general statements, definitions and prophetic statements in the Examples to describe the applicability of the genus claimed method. A written description, like a species, requires a specific description of the invention to show possession of the claimed generic method. The claim recites for a huge scope of a plurality (millions) of cells comprising different heterologous DNA sequences derived from a DNA library (collection of million compounds) that undergo immeasurable cell phenotypic changes. The disclosure fails to describe in specific terms the common attributes or characteristics that identify members of the heterologous DNA sequence derived from a genus DNA library in a plurality of cells. The instant case fails to provide sufficient descriptive information, such as definitive structural or functional features of the genus DNA library that comprise the

heterologous DNA. It also fails to describe the measurement of the electrophysiology of each cell as a result of expression of the heterologous DNA sequence.

Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed (genus) invention. See, e.g., Pfaff v. Wells Elecs., Inc., 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406; Amgen, Inc. v. Chugai Pharmaceutical, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991). A "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species; In re Ruschig, 379 F.2d 990, 995, 154 USPQ 118, 123 (CCPA 1967).

Claims 1-2 and 7-13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the

art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include:

(1) the breadth of the claims,
(2) the nature of the invention,
(3) the state of the prior art,
(4) the level of one of ordinary skill;
(5) the level of predictability in the art,
(6) the amount of direction provided by the inventor,
(7) the existence of working examples, and
(8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.
In re Wands, (U.S.P.Q. 2d 1400 (CAFC 1988).

1). The specification fails to give adequate direction and guidance in how to readily go about determining which DNA library from which the heterologous DNA can be derived, the derivation of said heterologous DNA, the components of said heterologous DNA. Also, there is a lack of direction as to the kind and/or number of cells that can express the heterologous DNA, the phenotypic change(s) or measurement of changes in the electrophysiology of each cell, the test agents and other numerous undefined variables of the broad claimed method.

2). The specification failed to provide working examples and provide only prophetic statements.

3). The breadth of the claims encompasses a large diversity of e.g., DNA that can be derived from any library, the components of a heterologous DNA, the cells expressing the heterologous DNA and the electrophysiology of said cells and phenotypic changes of said cell. It is well known in the art, that it is often difficult to determine whether a heterologous DNA is efficiently expressed by a particular expression system. And, it is not always easy to follow the expression of the heterologous DNA in particular cells; for example, to know whether or not a specific cell is expressing a member of the insert, especially for biological methods.

4). The state of the prior art is such that techniques are specifically applied for a predetermined heterologous DNA from a defined library.

5). The art is inherently unpredictable because it is not possible to predict which cells express the heterologous DNA for the electrophysiological measure of the cell.

6). Because the art is unpredictable, applicants' specification reasonably would not have assured persons skilled in the art that the numerous undefined variables used in the method result in identifying the heterologous DNA for measuring the cell changes without undue experimentation. Applicants do

not adequately enable persons skilled in the art to readily determine such. Applicants need not guarantee the success of the full scope of the claimed invention. However, skilled artisans are provided with little assurance of success.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-2 and 7-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. Claim 1 is indefinite as to how the different heterologous DNA is "derived" from a DNA library i.e., the means of its derivation. Step (iii) is unclear as to how the mere arrangement of the cells in the substrate permits detection of the electrophysiology of each cell. Step (iv) is unclear as to the differentiating characteristic of the "at least one cell of interest" and/or the "phenotypic change" exhibited by the cell of interest from the ones that are not desired. It is further unclear when the identification of the cell of interest is

determined simultaneously as a single entity or separately as recited in step(iv). There is no correspondence between the preamble and the body of the claims. The preamble recites only for performing electrophysiological measurements of cells. The body recites for identification by isolation of the genetic material, specifically mRNA. Step (iii) does not recite a cell of interest as claimed in step (iv) method of isolating the cell of interest.

2. Claim 2 is indefinite since claim 1 already appears to recite a sequenced genetic (DNA) material.

3. It is not clear as to the essentiality of a treating a cell with a test agent as recited in claims 9 and 10.

4. Claim 13 arrangement of the cells at "spaced-apart" location in or on the substrate is indefinite as to the measure or standard by which the distance (spaced) is apart. Furthermore, it is unclear how the spacing ***in or on*** the substrate is different from each other.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1-2 and 7 are rejected under 35 U.S.C. 102(e) as being anticipated by Qin (6994993).

Qin discloses at col. 20, line 1 up to col. 22, line 50:

> The present invention provides a whole cell or isolated cell membrane method to detect compound modulation of human .beta.1A sodium channel subunit.
>
> The method comprises the steps;
>
> 1) contacting a compound, and a cell or isolated cell membrane that contains functional human .beta.1A sodium channel subunit, and
>
> 2) measuring a change in the cell or isolated cell membrane in response to modified human .beta.1A sodium channel subunit function by the compound.

The amount of time necessary for cell or cell membrane contact with the compound is empirically determined, for example, by running a time course with a known human.beta.1A sodium channel subunit modulator and measuring cellular changes as a function of time.

The measurement means of the method of the present invention can be further defined by comparing a cell or cell membrane that has been exposed to a compound to an identical cell or cell membrane preparation that has not been similarly expose to the compound. Alternatively two cells, one containing functional human .beta.1A sodium channel subunit and a second cell identical to the first, but lacking functional human .beta.1A sodium channel subunit could be both used. Both cells or cell membranes are contacted with the same compound and compared for differences between the two cells. This technique is also useful in establishing the background noise of these assays. One of average skill in the art will appreciate that these control mechanisms also allow easy selection of cellular changes that are responsive to modulation of functional human .beta.1A sodium channel subunit.

Particularly preferred cell based assays (or cell membrane assays, if suitable) are those where the cell expresses an endogenous or recombinant sodium .alpha. channel subunit simultaneously with recombinant human .beta.1A. In these assays, a putative modulating compound can be analyzed for its effect on electrophysiological changes to the sodium flux upon the cell for altered expression of beta1A expression, or altered expression of the alpha/beta1A complex. Cells expressing recombinant human beta 1A are subjected to electrophysiological analysis to measure the total influx of sodium ions across the cell membrane by way of voltage differential using techniques well known by artisans in the field and described herein, including patch clamp voltage techniques as well as membrane proximal voltage sensitive dyes. Compounds that affect the proper function of human beta 1 may increase or decrease the capacity to open the Na channel, may increase or decrease the rate of Na influx (thus affect the change of membrane potential), may increase or decrease the rate of desensitization or re-sensitization of the channel. The term "test compound" or "modulating compound" as used

herein in connection with a suspected modulator of human beta1A refers to an organic molecule that has the potential to disrupt specific ion channel activity or cell surface expression of human beta 1A. For example, but not to limit the scope of the current invention, compounds may include small organic molecules, synthetic or natural amino acid peptides, proteins, or synthetic or natural nucleic acid sequences, or any chemical derivatives of the aforementioned.

The term "cell" refers to at least one cell, but includes a plurality of cells appropriate for the sensitivity of the detection method. Cells suitable for the present invention may be bacterial, yeast, or eukaryotic. For assays to which electrophysiological analysis is conducted, the cells must be eukaryotic, preferably selected from a group consisting of Xenopus oocytes, or PC12, COS-7, CHO, HEK293, SK-N-SH cells.

The assay methods to determine compound modulation of functional human sodium channel beta.1A subunit can be in conventional laboratory format or adapted for high throughput. The term "high throughput" refers to an assay design that allows easy analysis of multiple samples simultaneously, and capacity for robotic manipulation. Another desired feature of high throughput assays is an assay design that is optimized to reduce reagent usage, or minimize the number of manipulations in order to achieve the analysis desired. Examples of assay formats include 96-well or 384-well plates, levitating droplets, and "lab on a chip" microchannel chips used for liquid handling experiments. It is well known by those in the art that as miniaturization of plastic molds and liquid handling devices are advanced, or as improved assay devices are designed, that greater numbers of samples may be performed using the design of the present invention.

The cellular changes suitable for the method of the present invention comprise directly measuring changes in the function or quantity of human.beta.1A sodium channel subunit, or by measuring downstream effects of human beta.1A sodium channel subunit function, for example by measuring secondary messenger concentrations or changes in

transcription or by changes in protein levels of genes that are transcriptionally influenced by human beta.1A sodium channel subunit, or by measuring phenotypic changes in the cell. Preferred measurement means include changes in the quantity of human beta.1A sodium channel subunit protein, changes in the functional activity of human beta.1A sodium channel subunit, changes in the quantity of mRNA, changes in intracellular protein, changes in cell surface protein, or secreted protein, or changes in Ca+2, cAMP or GTP concentration. Changes in the quantity or functional activity of human.beta.1A sodium channel subunit are described herein. Changes in the levels of mRNA are detected by reverse transcription polymerase chain reaction (RT-PCR) or by differential gene expression. Immunoaffinity, ligand affinity, or enzymatic measurement quantitated changes in levels of protein in host cells. Protein-specific affinity beads or specific antibodies are used to isolate for example S-methionine labeled or unlabelled protein. Labeled protein is analyzed by SDS-PAGE. Unlabelled protein is detected by Western blotting, cell surface detection by fluorescent cell sorting, cell image analysis, ELISA or RIA employing specific antibodies. Where the protein is an enzyme, the induction of protein is monitored by cleavage of a fluorogenic or calorimetric substrate.

A preferred detection means for secreted proteins that are enzymes such as alkaline phosphatase or proteases, would be fluorescent or calorimetric enzymatic assays. Fluorescent/luminescent/color substrates for alkaline phosphatase are commercially available and such assays are easily adaptable to high throughput multiwell plate screen format. Fluorescent energy transfer based assays are used for protease assays. Fluorophore and quencher molecules are incorporated into the two ends of the peptide substrate of the protease. Upon cleavage of the specific substrate, separation of the fluorophore and quencher allows the fluorescence to be detectable. When the secreted protein could be measured by radioactive methods, scintillation proximity technology could be used. The substrate of the protein of interest is immobilized either by coating or incorporation on a solid support that contains a fluorescent material. A radioactive molecule, brought in close proximity to the solid phase by enzyme reaction, causes the fluorescent material to become excited and emit

visible light. Emission of visible light forms the basis of detection of successful ligand/target interaction, and is measured by an appropriate monitoring device. An example of a scintillation proximity assay is disclosed in U.S. Pat. No. 4,568,649, issued Feb. 4, 1986. Materials for these types of assays are commercially available from Dupont NEN.RTM. (Boston, Mass.) under the trade name FlashPlate.TM..

A preferred detection means where the endogenous gene results in phenotypic cellular structural changes is statistical image analysis the cellular morphology or intracellular phenotypic changes. For example, but not by way of limitation, a cell may change morphology such a rounding versus remaining flat against a surface, or may become growth-surface independent and thus resemble transformed cell phenotype well known in the art of tumor cell biology, or a cell may produce new outgrowths. Phenotypic changes that may occur intracellularly include cytoskeletal changes, alteration in the endoplasmic reticulum/Golgi complex in response to new gene transcription, or production of new vesicles.

The present invention is also directed to methods for screening for compounds that modulate the expression of DNA or RNA encoding Human beta.1A sodium channel subunit as well as the function of Human beta.1A sodium channel subunit protein in vivo. Compounds may modulate by increasing or attenuating the expression of DNA or RNA encoding a Human beta.1A sodium channel subunit, or the function of a Human beta.1A sodium channel subunit protein. Compounds that modulate the expression of DNA or RNA encoding a Human beta.1A sodium channel subunit or the function of a Human beta.1A sodium channel subunit protein may be detected by a variety of assays. The assay may be a simple "yes/no" assay to determine whether there is a change in expression or function. The assay may be made quantitative by comparing the expression or function of a test sample with the levels of expression or function in a standard sample. Modulators identified in this process are useful as candidate therapeutic agents.

> Following expression of the Human beta.1A sodium channel subunit in a recombinant host cell, the Human beta.1A sodium channel subunit protein may be recovered to provide the purified Human beta.1A sodium channel subunit in active form. Several Human beta.1A sodium channel subunit purification procedures are available and suitable for use. As described above for purification of Human beta.1A sodium channel subunit from natural sources a recombinant Human beta.1A sodium channel subunit may be purified from cell lysates and extracts, or from conditioned culture medium, by various combinations of, or individual application of salt fractionation, ion exchange chromatography, size exclusion chromatography, hydroxylapatite adsorption chromatography and hydrophobic interaction chromatography, lectin chromatography, and antibody/ligand affinity chromatography.

See also the abstract and the specific steps of the method in the Examples starting at col. 29, Example 1.

Claims 1-2 and 7 are rejected under 35 U.S.C. 102(e) as being anticipated by Gillespie (6936457).

Gillespie discloses at col. 5, line 1 up to col. 21, starting at Example 1:

> Methods to determine the presence and/or activity of human neuronal nicotinic AChRs include assays that measure nicotine binding, Rb ion-flux, Ca influx, the electrophysiological response of cells, the electrophysiological response of oocytes transfected with RNA from the cells, and the like. In particular, methods are provided herein for the measurement or detection of an AChR-mediated response upon contact of cells containing the DNA or mRNA with a test compound.
>
> As used herein, a recombinant or heterologous human neuronal nicotinic AChR refers to a receptor that contains one or more subunits encoded by heterologous DNA that has been introduced into and expressed in cells capable of

expressing receptor protein. A recombinant human neuronal nicotinic AChR may also include subunits that are produced by DNA endogenous to the host cell. In certain embodiments, recombinant or heterologous human neuronal nicotinic AChR may contain only subunits that are encoded by heterologous DNA.

As used herein, heterologous or foreign DNA and RNA are used interchangeably and refer to DNA or RNA that does not occur naturally as part of the genome of the cell in which it is present or to DNA or RNA which is found in a location or locations in the genome that differ from that in which it occurs in nature. Typically, heterologous or foreign DNA and RNA refer to DNA or RNA that is not endogenous to the host cell and has been artificially introduced into the cell. Examples of heterologous DNA include DNA that encodes a human neuronal nicotinic AChR subunit, DNA that encodes RNA or proteins that mediate or alter expression of endogenous DNA by affecting transcription, translation, or other regulatable biochemical processes, and the like. The cell that expresses heterologous DNA may contain DNA encoding the same or different expression products.

As used herein, a functional neuronal nicotinic AChR is a receptor that exhibits an activity of neuronal nicotinic AChRs as assessed by any in vitro or in vivo assay disclosed herein or known to those of skill in the art. Possession of any such activity that may be assessed by any method known to those of skill in the art and provided herein is sufficient to designate a receptor as functional. Methods for detecting NAChR protein and/or activity include, for example, assays that measure nicotine binding, Rb ion-flux, Ca influx, the electrophysiological response of cells containing heterologous DNA or mRNA encoding one or more receptor subunit subtypes, and the like.

It has been found that not all subunit subtypes are expressed in all neural tissues or in all portions of the brain. Thus, in order to isolate cDNA encoding particular subunit subtypes or splice variants of such subtypes, it is preferable to screen libraries prepared from different neuronal or neural tissues.

Exemplary cells for introducing DNA include cells of mammalian origin (e.g., COS cells, mouse L cells, Chinese hamster ovary (CHO) cells, human embryonic kidney cells, African green monkey cells and other such cells known to those of skill in the art).

DNA may be stably incorporated into cells or may be transiently introduced using methods known in the art. Stably transfected mammalian cells may be prepared by transfecting cells with an expression vector having a selectable marker gene (such as, for example, the gene for thymidine kinase, dihydrofolate reductase, neomycin resistance, and the like), and growing the transfected cells under conditions selective for cells expressing the marker gene. To produce such cells, the cells should be transfected with a sufficient concentration of subunit-encoding nucleic acids to form human neuronal nicotinic AChRs that contain the human subunits encoded by heterologous DNA. The precise amounts and ratios of DNA encoding the subunits may be empirically determined and optimized for a particular combination of subunits, cells and assay conditions. Recombinant cells that express neuronal nicotinic AChR containing subunits encoded only by the heterologous DNA or RNA are especially preferred.

Heterologous DNA may be maintained in the cell as an episomal element or may be integrated into chromosomal DNA of the cell. The resulting recombinant cells may then be cultured or subcultured (or passaged, in the case of mammalian cells) from such a culture or a subculture thereof. Methods for transfection, injection and culturing recombinant cells are known to the skilled artisan. Similarly, the human neuronal nicotinic AChR subunits may be purified using protein purification methods known to those of skill in the art. For example, antibodies or other ligands that specifically bind to one or more of the subunits may be used for affinity purification of the subunit or human neuronal nicotinic AChRs containing the subunits.

DNA encoding human neuronal nicotinic AChR alpha and beta subunits may be isolated by screening suitable human cDNA or human genomic libraries under suitable hybridization conditions with DNA disclosed herein (including nucleotides

> derived from any of SEQ. ID. Nos:1, 3, 5, 7, 9, 11, 13, 15 or 17, or with any of the deposited clones referred to herein. Suitable libraries can be prepared from neuronal tissue samples, hippocampus tissue, or cell lines, such as the human neuroblastoma cell line IMR32 (ATCC Accession No. CCL127), and the like. The library is preferably screened with a portion of DNA including the entire subunit-encoding sequence thereof, or the library may be screened with a suitable probe.

Claims 1-2 and 7-13 are rejected under 35 U.S.C. 102(e) as being anticipated by Maher (6969449)

Maher discloses at e.g., col. 12, line 30 up to the Examples, particularly Example 10:

> As a non-limiting introduction to the breadth of the invention, the invention includes several general and useful aspects, including:
>
> 1) Instrumentation including electrodes, and electrode arrays for reliably generating uniform electrical fields in cultures of living cells in aqueous solution.
>
> 2) Multiwell plates comprising surface electrodes for high throughput and miniaturized stimulation and analysis of ion channel or cellular activities.
>
> 3) Systems for high throughput analysis of ion channel and cellular activities and for use in drug discovery, analysis, screening and profiling.
>
> 4) Methods for modulating the transmembrane potential of a living cell via the use of repetitive electrical stimulation.
>
> 5) Methods for screening the effects of test compounds on the activities of voltage regulated, and non-voltage

regulated ion channels, transporters and leak currents. Including determining state-dependent pharmacological activity of compounds against ion channel and transporter proteins.

6) Methods for profiling and selecting cells or clones based on their response to electrical stimulation.

7) Methods for quantitative determination of cellular and ion channel parameters in a high-throughput manner, and for quantification of the pharmacological effects of compounds on those parameters.

8) Methods for the introduction of exogenous compounds into the intracellular spaces of cells.

9) Methods for modulating the transmembrane potential of intracellular organelles, and for screening test compounds against ion channels in these organelles.

10) Methods for characterizing the physiological effect of the transmembrane potential on the function and regulation of physiological and biochemical responses, including gene expression, enzyme function, protein activity and ligand binding.

11) Methods for programming or training adaptive neuronal networks or bio-computers for specific functional or logical responses.

12) Methods for providing efficient neuronal interfaces for prosthetic devices implanted into an animal, including a human.

Selection of stable clones will typically be made on the basis of successful expression of the ion channel of interest at sufficient level to enable it's facile detection. In many cases this analysis will require functional characterization of individual clones to identify those that exhibit appropriate electrophysiological characteristics consistent with

expression of the clone of interest. This analysis can be completed via the use of patch clamping, or via the measurement of transmembrane potentials using transmembrane potential sensitive dyes as described below.

The invention also provides non-human animals expressing one or more hybrid olfactory receptor sequences of the invention, particularly human olfactory receptor sequences. Such expression can be used to determine whether a test compound specifically binds to a mammalian olfactory transmembrane receptor polypeptide in vivo by contacting a non-human animal stably or transiently infected with a nucleic acid derived from the library of the invention with a test compound and determining whether the animal reacts to the test compound by specifically binding to the receptor polypeptide.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to T. D. Wessendorf whose telephone number is(571) 272-0812. The examiner can normally be reached on Flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached on (571) 272-0765. The fax phone number for the organization where this application or proceeding is assigned is 571 273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

T. D. Wessendorf
Primary Examiner
Art Unit 1639

tdw
March 30, 2007